UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/462,993	04/17/2000	MARIE-PAULE KIENY	017753-122	5746

7590 05/17/2004

NORMAN H STEPNO
BURNS DOANE SWECKER & MATHIS
PO BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 05/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/462,993	Kieny, Marie-Paule	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-63 and 65-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-63 and 65-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/12/04 has been entered.

The amendment filed on 12/16/03 has been entered. Claim 65 has been canceled. Claims 44, 45, 47, 49, 51, 62, 73, and 80 have been amended. Claims 44-64 and 66-82 as submitted (or renumbered claims 44-63 and 65-81) are pending in the application, and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated.

Specification

The disclosure is objected to because of the following informalities: The specification does not contain a section of "Brief Description of Drawings" (See MPEP 608.01(f)). Inserting the subtitle before line 29 of page 27 would obviate this objection.

The disclosure is objected to because of the language of the abstract. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc. (emphasis added).

Appropriate correction is required.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). It is noted that the amendment submitted November 2001 included new claims 44-63, wherein claim 55 was missing and has been missing since. Misnumbered claims 56-82 are now renumbered as 55-81. The following Office action is issued according to the renumbered claims. Any subsequence amendment submitted by the applicant should reflect such change.

The amended claims 44 and 45 recite, "the E6 and E7 early region of a HPV-16 papillomavirus genome". However, applicants do not specifically point out the support in the specification for such recitation, and the specification as originally filed does not

appear to use this term. Replacing the phrase with "selected from the group consisting of E6 or E7 polypeptide of HPV-16" may obviate this objection.

Claim 49 is objected to because of claim language "having". It is suggested to replace "having" with "comprising".

Claim 61 is objected to because an article should precede "sequence" in lines 3 and 4 of "(1), (2), and (3)" respectively.

Claim 62 and 67 are objected to because the recited "compound" should be replaced with "polypeptide".

Claims 63, 66, 68, 69, 77 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-48, 50-60, 65, 70, 71, 76, 78-81 are newly rejected under 35U.S.C. 112 first paragraph, because the specification as originally filed does not describe the invention as now claimed. The original disclosure fails to specify the term "non-integrative vector" as now claimed. The term is now considered to be new matter.

MPEP 2163.02 teaches that "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN INVENTION THAT IS CLEARLY CONVEYED TO THOSE SKILLED IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY NOT PRESENT IN THE APPLICATION AS

FILED, INVOLVING A DEPARTURE FROM, ADDITION TO, OR DELETION FROM THE DISCLOSURE OF THE APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added). In the instant case, the specification as originally filed describes various genetic constructs and recombinant viral vectors including poxviral and retroviral vectors (e.g. Specification, pages 25-26). The later submitted claim 44 recites "non-integrative vector", however, the specification fails to define the term and applicants failed to specifically point out the support for such recitation. Thus, the amendment is a departure from or an addition to the disclosure of the application as filed, accordingly, it introduces new matter into the disclosure.

For reasons set forth above, the amendment is objected to under 35 U.S.C. §132 because it introduces new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention. Applicant is required to cancel the new matter in the reply to this Office Action.

To the extent that the claimed subject matters are not adequately described in the instant disclosure, claims 44-48, 50-60, 65, 70, 71, 76, 78-81 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention,

since a disclosure cannot teach one to make or use something that has not been adequately described.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44-48, 50-60, 65, 70-76, 78-81 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 is vague and indefinite because of the phrase starting "which is modified...". It is unclear what subject the phrase describes, "genome" or "immunogenic polypeptide" or "a sequence", thus, the metes and bounds of the claims are uncertain.

Claim 46 is vague and indefinite because of the claim recitation, "and/or".

Claims 47, 59, 60, 72 are directed to modified HPV-E6 or E7 polypeptides with specific residues being deleted. However, since there are many different sequences of HPV-E6 or E7 such as listed in NCBI database (see enclosure), it is unclear, which of these sequences the claims refer to, thus, the metes and bounds of the claims are uncertain. Amending the claims to include a sequence identifier would overcome the rejection.

Claim 47 recites the limitation "said E6 polypeptide". There is insufficient antecedent basis for this limitation in the claim.

Claim 55 recites "at least one of *said polypeptides* is a polypeptide as defined in claim 44". However, claim 44 is directed to a modified polypeptide, which starts with "at

least one immunogenic polypeptide" (line 3). It is unclear which polypeptide claim 55 refers to, thus, the metes and bounds of the claim are uncertain. If the recited "said polypeptide" of claim 55 refers to the "immunogenic polypeptide", then it fails to further limit the previous claims since it encompasses more polypeptides compared to the base claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 44, 46, 48, 50-56, 70, 71, 78 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Andrew et al* (J Virol 1990;64:4776-83), in view of *Boursnell et al* (Vaccine 1996;14:1485-94), *Borysiewicz et al* (Lancet 1996 Jun;347:1523-7), and *Stanley et al* (US 6,096,869).

Andrew et al teach a method of modifying a non-secretive viral antigen (VP7) for enhancing immunogenicity, the method comprises making a composition comprising a

vaccinia viral vector (poxvirus) expressing a chimeric protein comprising the coding sequence of VP7 plus the signal peptide (a secretory sequence) and transmembrane anchor sequences from the influenza virus HA (e.g. 1st paragraph, right column, page 4776), inoculating rabbits with the vaccinia viruses intradermally (injectable pharmaceuticals), and obtaining an enhanced antibody production as well as elevated T-cell response compared to the intracellular and secreted forms of the antigen (e.g. 1st paragraph, page 4781). *Andrew et al* teach that it has proven difficult to generate good immune response against antigens that are not normally expressed on the surfaces of the infected cells and the most immunogneic antigens have been the cell surface-expressed glycoproteins from enveloped viruses such as the rabies virus glycoprotein G. *Andrew et al* go on to teach by adding secretory signal and/or membrane anchor domain, significant improvement could be observed for the previously poor or moderate immunogenic antigens (left column, page 4776). They then concluded that cell surface anchoring might provide a strategy to increase the immunogenicity of intracellular antigens from other viruses (e.g. abstract).

The teaching of *Andrew et al* differs from instant claimed invention in that it does not particularly teach the E6 and E7 polypeptide of HPV-16. *Boursnell et al* supplement *Andrew et al* by disclosing a composition for cancer therapy comprising a recombinant vaccinia virus expressing E6 and E7 proteins from HPV16, and induced CTL response in intranasal inoculated mice (e.g. page 1492). *Boursnell et al* teach that E6 and E7 proteins are intracellular proteins, whereas the immune effector mechanism for cancer is likely to be CTL for antigens expressed on the surface of the tumor cells,

nonetheless, E6 and E7 could act as targets for CTL-mediated tumor cell killing (paragraph bridging pages 1485-6). *Boursnell et al* go on to teach that studies have shown that effective anti-tumor responses can be induced by vaccination even where the tumor cells themselves are poorly immunogenic, and indicated that a clinical study is underway (Discussion). In a subsequence publication (*Borysiewicz et al*), they teach that the CTL response was indeed induced in a few but not all patients.

The combined teaching of *Andrew et al* and *Boursnell et al* differs from instant claimed invention in that it does not teach including a cytokine in the composition. *Stanley et al* supplement the teaching of *Andrew et al* and *Boursnell et al* by disclosing the therapeutic effect of cytokines particularly IL-12 on diseases associated with HPV infection and proliferation (tumor). *Stanley et al* teach, "THE PRESENT INVENTION ARISES FROM A SURPRISING FINDING THAT IL-12 IS PRESENT IN 100% OF REGRESSING HPV-INDUCED TUMORS SURVEYED BY THE PRESENT INVENTORS IN A CLINICAL STUDY" (column 2, lines 48-49). *Stanley et al* go on to teach a pharmaceutical composition comprising a combination of IL-12 and a HPV antigen including E6 and E7 of HPV16, and late proteins of HPVs (column 4, lines 2-3), wherein the proteins can be carried by recombinant viral vectors (column 3, left column).

The teaching of *Andrew et al* established that it is known to the skilled artisan to enhance antigenicity by making a chimeric protein comprising a secretory signal and a membrane anchoring sequence. *Boursnell et al* established that it is known to the skilled artisan that the E6 and E7 of HPV-16 are candidate proteins for recombinant virus induced, CTL-mediated tumor cell killing, and such effect needs further

improvement. The teaching of *Stanley et al* established that it is known to the skilled artisan to use cytokine such as IL-12 for enhanced anti-HPV and anti-tumor effects.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the E6 and E7 polypeptides as taught by *Boursnell et al* with the signal peptide and membrane anchoring sequence as taught by *Andrew et al* and include a cytokine adjuvant and/or late HPV proteins in the composition as taught by *Standley et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because it would enhance the antitumor effect of the composition. Given the clinical observation of limited success using unmodified E6 and E7 of HPV-16 in mouse and humans as taught by *Boursnell et al, Borysiewicz et al,* and *Stanley et al*, the skilled artisan would have had a reasonable expectation of success in treating HPV-associated tumors with the modified E6 and E7 and including a cytokine such as IL-12 in the composition. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 65 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Andrew et al* (J Virol 1990;64:4776-83), *Boursnell et al* (Vaccine 1996;14:1485-94), *Borysiewicz et al* (Lancet 1996 Jun;347:1523-7), and *Stanley et al* (US 6,096,869) as applied to claims 44, 46, 48, 50-56, 70, 71, 78 above, and further in view of *Sutter et al* (Vaccine 1994;12:1032-40).

Andrew et al and *Boursnell et al* teach using a recombinant vaccinia virus for HPV vaccination, *Stanley et al* teach using attenuated live virus (column 7, line 51). The combined teachings of *Andrew et al*, *Boursnell et al*, *Borysiewicz et al*, and *Stanley et al* however, do not specify the attenuated vaccinia virus MVA.

Sutter et al supplement the above teaching by disclosing the highly attenuated and safety-tested MVA and its use in developing protective immunity to influenza virus in mice, and establish that it is well known in the art to use MVA as a vaccine carrier at the time the instant application was filed.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition as taught by *Andrew et al*, *Boursnell et al*, *Borysiewicz et al*, and *Stanley et al* with that of *Sutter et al* by simply substituting the recombinant vaccinia viral vector with the modified version, i.e. MVA with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because MVA has proven to be safe and effective as a vaccine carrier. Given the success observed in influenza virus vaccine as taught by *Sutter et al*, and the limited success observed by *Boursnell et al, Borysiewicz et al,* and *Stanley et al,* the skilled artisan would have had a reasonable expectation of success in combining the elements in the HPV vaccine composition. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

Claims 45, 47, 49, 57-63, 66-69, 72-75, 77, 79-81 appear to be free of the cited prior art of record, however, they are subject to other rejections and objections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist **Rena Jones** whose telephone number is **571-272-0571**.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QL
May 13, 2004